POSTER 1936

Trial in Progress: Linvoseltamab (REGN5458), a BCMAxCD3 Bispecific Antibody, in a Phase 1b Multi-Cohort Study of Combination Regimens for Patients with Relapsed/Refractory Multiple Myeloma

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Background

Multiple myeloma (MM)

- Despite the increased effectiveness of combination drug therapy, MM remains incurable, and patients eventually succumb to relapsed disease[1]
- With each subsequent line of therapy, relapsed/refractory MM (RRMM) becomes more challenging to treat, as high-quality responses become harder to achieve[2,3]
- Therefore, there remains a significant unmet need for new combination regimens that leverage drugs with novel mechanisms of action to improve outcomes in MM

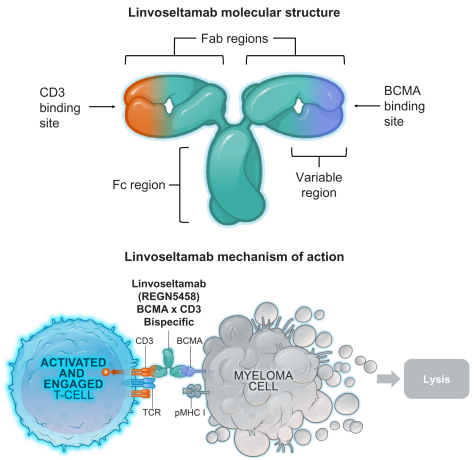
B-cell maturation antigen (BCMA)

- BCMA is a cell surface protein expressed on malignant plasma cells[3]
- Notably, BCMA is detected only at low levels on normal plasma cells, activated B cells, and plasmacytoid dendritic cells, making it an attractive therapeutic target for MM[4]

Linvoseltamab (REGN5458)

- Linvoseltamab is a bispecific antibody capable of binding to BCMA on MM cells and cluster of differentiation 3 on T cells, inducing targeted T-cell-mediated cytotoxicity of MM cells (**Figure 1**)
- Results from a Phase 1 dose-escalation study of linvoseltamab monotherapy in patients with RRMM showed early, deep, and durable responses with a manageable safety and tolerability profile (NCT03761108)[5]
  - Among patients treated at the 200–800 mg dose levels, the response rate was 75%
  - Cytokine release syndrome was reported in 38% of patients; the severity was mostly Grade 1 with no Grade ≥3 events
- Given the encouraging early efficacy and limited overlapping toxicity of linvoseltamab, it is reasonable to explore the potential benefit of combining linvoseltamab with other anti-myeloma agents, with the aim of improving the depth and duration of responses

Figure 1. Linvoseltamab structure and mechanism of action



BCMA, B-cell maturation antigen; CD, cluster of differentiation; Fab, antigen-binding fragment; Fc, crystallizable fragment; pMHC I, peptide major histocompatibility complex type I; TCR, T-cell receptor.

Study Design and Methods

Design and objectives

- This global, Phase 1b, open-label, multi-cohort umbrella study (LINKER-MM2; NCT05137054) is designed to assess the safety, tolerability, and preliminary efficacy of linvoseltamab in combination with other cancer treatments in patients with RRMM
- Each combination will be evaluated in a separate cohort
- Each cohort will include a dose-finding portion to select an appropriate linvoseltamab dose, followed by a dose-expansion portion
- The primary objectives are to assess the safety and tolerability, as well as identify the recommended Phase 2 dose of linvoseltamab in combination with various other systemic cancer treatments
- Secondary objectives for each cohort include assessments of preliminary antitumor activity by International Myeloma Working Group criteria[6], depth and durability of response, pharmacokinetics, immunogenicity of linvoseltamab, and overall survival
- The study will take place at approximately 50 global sites

Population

- Approximately 210 patients are anticipated to enroll in this study
- Key inclusion and exclusion criteria are listed in **Table 1**

Table 1. Selected inclusion and exclusion criteria

Key inclusion criteria
• Age ≥18 years
• ECOG PS ≤1
• Adequate organ function
• Progressive RRMM and one of the following: ○ **Cohorts combining linvoseltamab with an approved anti-myeloma agent:** ▪ ≥3 lines of therapy **OR** ▪ ≥2 lines of therapy and either: • Prior exposure to at least 1 PI, 1 IMiD, and 1 anti-CD38 antibody • Double-refractory to 1 PI and 1 IMiD, or the combination of 1 PI and 1 IMiD ○ **Cohorts combining linvoseltamab with an investigational agent:** ▪ ≥3 lines of therapy and exposure to at least 1 anti-CD38 antibody, 1 IMiD, and 1 PI **OR** ▪ Triple-class refractory disease (anti-CD38 antibody, IMiD, PI)
• Measurable disease per IMWG consensus criteria[6]
Key exclusion criteria
• Patients with known MM brain lesions or meningeal involvement
• Treatment with any systemic anti-myeloma therapy within 5 half-lives or 21 days prior to first administration of study drug regimen, whichever is shorter
• Prior treatment with a BCMA-directed bispecific antibody or BCMA-directed CAR-T (BCMA antibody-drug conjugates are permitted)
• History of allogeneic SCT or autologous SCT within 12 weeks of the start of study treatment
• History of neurodegenerative condition or CNS movement disorder or seizure within 12 months prior to study enrollment
• Live or attenuated vaccination within 28 days prior to first study drug regimen administration with a vector that has replicative potential
• Cardiac ejection fraction <40% by ECHO or MUGA scan

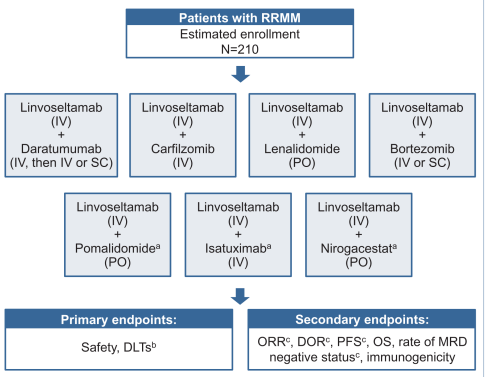
BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell therapy; CD, cluster of differentiation; CNS, central nervous system; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; IMiD, immunomodulatory imide drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; MUGA, multigated acquisition; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma; SCT, stem cell transplantation.

- Prior exposure to the cohort-specific combination agent is allowed if previously tolerated at the approved full dose
  - Some cohorts will exclude patients that are refractory to the combination agent from the dose expansion portion
  - Patients must undergo a minimum washout period following prior treatment with the cohort-specific combination agent

Treatment

- Linvoseltamab will be used in combination with other therapies in patients with RRMM
- Each cohort will assess a separate combination regimen of linvoseltamab plus an approved or investigational agent (**Figure 2**)

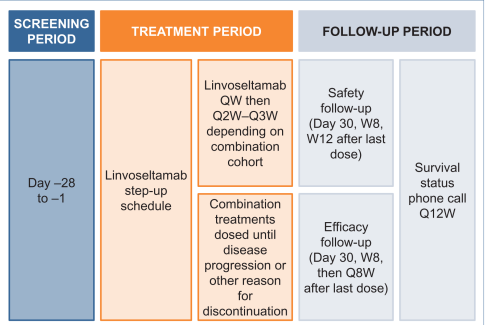
Figure 2. Overview of study design



[a]Planned expansion cohort. [b]Dose escalation only. [c]As measured using IMWG consensus criteria.

DLT, dose-limiting toxicity; DOR, duration of response; IMWG, International Myeloma Working Group; IV, intravenous; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral; RRMM, relapsed/refractory multiple myeloma; SC, subcutaneous.

Figure 3. Overview of study treatments



Q2/3/8/12W, once every 2/3/8/12 weeks; QW, weekly; W, week.

- Linvoseltamab will be administered intravenously on a weekly basis starting with a step-up dosing schedule (**Figure 3**)
  - After 15–16 weeks, the dosing frequency will be reduced to every 2–3 weeks depending on the cohort
- The other cancer treatments will be administered at the approved doses
- All regimens will be given until disease progression or any other reason for discontinuation

Endpoints

- The primary and secondary endpoints for each cohort are shown in **Table 2**
- There is no formal statistical hypothesis for this study
- The results will be reported in a descriptive manner

Table 2. Study endpoints for each cohort

Primary endpoints	
Dosing finding	**Dose expansion**
• Incidence of DLTs from the first dose of study drug to the end of the DLT observation period • Incidence and severity of TEAEs and AESIs through study completion	• Incidence and severity of TEAEs and AESIs through study completion
Secondary endpoints	
• ORR, DOR, PFS, and proportion of participants achieving MRD-negative status measured using IMWG consensus criteria • Pharmacokinetics • Immunogenicity • OS	

AESI, adverse event of special interest; DOR, duration of response; DLT, dose-limiting toxicity; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

Implications

- **When complete, this umbrella study will provide important information on the tolerability and preliminary clinical efficacy of linvoseltamab (REGN5458) when given in combination with other cancer therapies to treat patients with RRMM**

References

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